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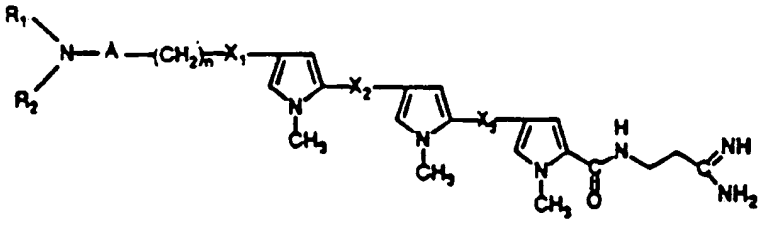
(54) Title: RETROREVERSE PYRROLE-AMIDINO OLIGOPEPTIDE ANTICANCER AGENT ANALOGUES, PREPARATION OF SAME, AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH ANALOGUES



(I)

(57) Abstract

A description is given of compounds as per general formula (I), and of pharmaceutically acceptable salts thereof, active as anticancer and antivirus agents.

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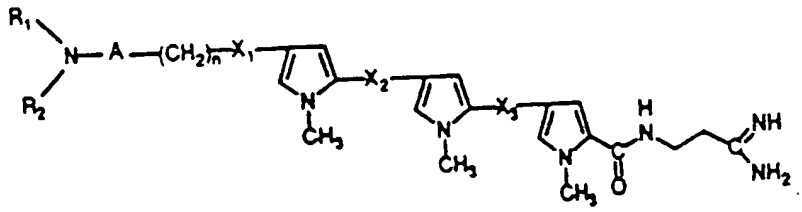
Retroreverse pyrrole-amidino oligopeptide anticancer agent analogues, preparation of same, and pharmaceutical compositions containing such analogues.

Field of the Invention

The present invention relates to anticancer agents as per general formula (I)



(I)

and pharmaceutically acceptable salts thereof,

where:

n = 0 or a whole number from 1 to 6

A = a single chemical bond or an alicyclic or aromatic or heterocyclic residue,

X_1 = a chemical bond, the -NHCO- group or the -CONH- group

X_2, X_3 (either equal or different) = the -CONH- or -NHCO- group

and where:

i) R_1 and R_2 (equal) = an oxiranomethyl or 1-aziridinomethyl or C_2-C_4 alkyl group, substituted in position 2, if required, by a hydroxy or C_2-C_4 alcoxy halogen or $-OSO_2R_4$ group, where:

R_4 is C_1-C_4 alkyl or phenyl

or

ii) R_1 = H, R_2 as defined above

or

iii) R_1 = H, R_2 = $-CO-(CH_2)_m-R_3$, where m is 0 or a whole number from 1 to 4 and R_3 = halogen, oxiranyl or methyloxiranyl or azirinidyl, cyclopropyl or a C_2-C_6 alkenyl group substituted, if required, by halogens or a ketone or an α,β unsaturated alicylic lactone.

Considering that:

if R_1 and R_2 are as defined under i) and ii) and X_1 is a single chemical bond, A is a single chemical bond and n = 0;

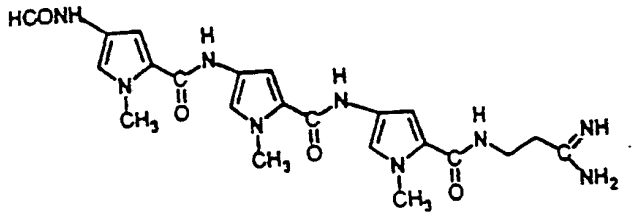
if R_1 and R_2 are as defined under iii), X_1 and A are single chemical bonds and n = 0;

if X_1 is a single chemical bond or the -CONH- group and n = 0, X_2 = X_3 = -CONH- is impossible.

The invention further refers to the process for the preparation of the aforesaid products, the pharmaceutically acceptable salts thereof, and the pharmacetical compositions containing said products.

State of the art

Dystamicin is an antibiotic already known having formula (A)



(A)

belonging to the pyrrole-amidino antibiotic group, endowed with

interesting antiviral properties, e.g. against herpesviruses and Moloney sarcoma virus, and capable of interacting reversibly and selectively with dA and dT base-rich DNA sequences, thus interfering both in replication and transcription processes (cf. F. Arcamone, Molecular basis of specificity in nucleic acid-drug interaction, B. Pullman and J. Jorterez, eds., 369-383 (1990), Kluwer Academic Publishers).

As known, the severe side effects that, at present, are caused by the intake of antiviral and anticancer agents limit their use in a large number of cases, which, instead, should benefit from the therapy. Moreover, the clinical treatment of serious solid tumours, e.g. of lungs and ovaries, must be developed, as none - for the time being - is adequate.

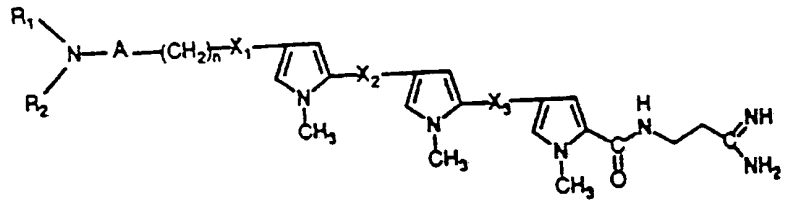
A requisite for the therapeutic progress in this field is, therefore, the discovery of compounds having molecular characteristics increasing their selectivity in inhibiting the proliferation of viruses and tumoural cells in respect of the healthy ones.

Detailed description of the invention

An object of this invention is the obtainment of anticancer and antiviral compounds and in particular of dystamicin analogues in which one or more carboxyamidic bonds has/have been replaced by a retrocarboxyamidic bond, containing new chemical modifications at the N-terminal side chain. The said compounds have shown a high anticancer and antiviral activity and a high selectivity in

inhibiting tumoural cells and viruses in respect of healthy cells.

The compounds as per the present invention are compounds as per general formula (I) and pharmaceutically acceptable salts thereof:



(I)

where:

n = 0 or a whole number from 1 to 6

A = a single chemical bond or an alicyclic or aromatic or heterocyclic residue,

X_1 = a single chemical bond, the -NHCO- group or the -CONH- group

X_2, X_3 (either equal or different) = the -CONH- or -NHCO- group

and where:

i) R_1 and R_2 (equal) = an oxiranomethyl or 1-aziridinomethyl or C_2-C_4 alkyl group, substituted in position 2, if required, by a hydroxy or C_2-C_4 alcoxy halogen or an $-OSO_2R_4$ group, where:

R_4 is C_1-C_4 alkyl or phenyl

or

ii) R_1 = H, R_2 as defined above

or

iii) R_1 = H, R_2 = $-CO-(CH_2)_m-R_3$, where m is 0 or a whole number from 1 to 4 and R_3 = halogen, oxiranyl or methyloxiranyl or azirinidyl, cyclopropyl or a C_2-C_6 alkenyl group substituted, if required, by

halogens or a ketone or an α,β unsaturated alicylic lactone.

Considering that:

if R_1 and R_2 are as defined under i) and ii) and X_1 is a single chemical bond, A is a single chemical bond and n = 0;

if R_1 and R_2 are as defined under iii), X_1 and A are single chemical bonds and n = 0;

if X_1 is a single chemical bond or the -CONH- group and n = 0, X_2 = X_3 = -CONH- is impossible.

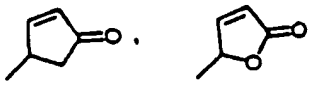
The invention also refers to pharmaceutical compositions containing the aforesaid compounds or the pharmaceutically acceptable salts therof, based on inorganic acids, e.g. hydrochloric or hydrobromic or sulphuric or nitric acids, etc., or on organic acids, e.g. acetic or propionic or succinic or malonic or citric or tartaric or methanesulfonic or p-toluenesulfonic acids, etc.

According to the present invention, the compounds as per formula (I) are preferred, where:

n is as defined above

A is a single cyclohexyl or p-phenyl or 1-methylpyrrole or thiophene or thiazole or imidazole or furan or isoxazole or oxazole or triazole or pyridine or pyrrole chemical bond

R_1 and R_2 (when R_2 is not $-CO-(CH_2)_m-R_3$) preferably stand for an ethyl or 2-chloroethyl or methanesulfonylethyl and when R_2 = $-CO-(CH_2)_m-R_3$, R_3 preferably stands for chlorine or bromine, or a 3-methyloxyranyl or ethenyl or 1-chloroethenyl or 1-bromoethenyl group



where:

m = 0, 1, 2,

X_1, X_2, X_3 are as defined above.

Particularly preferred are the following compounds:

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]benzenecarboxyamido]pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]benzeneaminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]benzeneaminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]benzenecarboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]thiophene-2-carboxyamido]pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[N,N-bis(2-chloroethyl)-amino]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[N,N-bis(2-chloroethyl)-

amino]pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[N,N-bis(2-chloroethyl)-amino]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[N,N-bis(2-chloroethyl)-amino]pyrrole-2-aminocarbonyl]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[6-[4-[N,N-bis(2-chloroethyl)-amino]phenyl]hexaneaminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-(3-methyloxirano-carbonylamino)pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-(cyclopropylcarbonylamino)pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-aziridino) carbonylamino]pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-(α-chloroacrylamido)pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[2[4-[N,N-bis(2-chloroethyl)-amino]phenyl]ethanaminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-

carboxyamido]pyrrole-2-carboxyamido] propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]benzylaminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

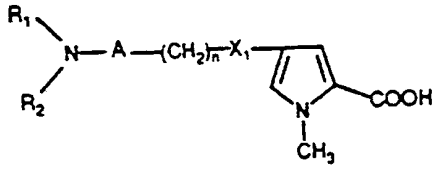
3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[3-[4-[N,N-bis(2-chloroethyl)-amino]-phenyl]propanamino-carbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[4-[N,N-bis(2-chloroethyl)-amino]-phenyl]butanamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

N-deformyl-N-[4-[4-[N,N-bis(2-chloroethyl)amino]phenyl] butanoyl]dystamicin hydrochloride.

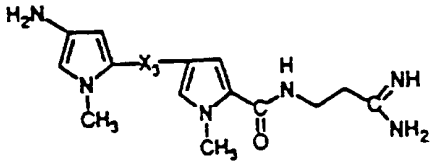
The compounds as per general formula (I) may be prepared on the basis of the following processes:

a) Reaction of compound as per formula (II)



(II)

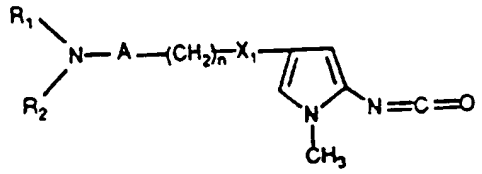
where n, A, R_1, R_2 and X_1 are as defined above, or a reactive derivative thereof, with compound as per formula (III)



(III)

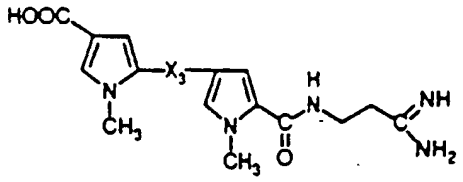
where X_3 is as defined above, to obtain compounds as per formula (I) where X_2 = -CONH- and A, n, R_1, R_2, X_1 and X_3 are as defined above.

b) Reaction of compound as per formula (IV)



(IV)

where n, A, R_1, R_2 and X_1 are as defined above, or a reactive precursor of same, with compound as per formula (V)



(V)

where X_3 is as defined above, to obtain compounds as per formula (I), where X_2 = -NHCO- and A, n, R_1, R_2, X_1 and X_3 are as defined above.

The reaction of compound as per formula (II) with compound as per formula (III) was conducted in the presence of condensers, such as DCC (dicyclohexyl carbodiimide) or EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] either in the presence or in the absence of hydroxybenzotriazole or BOP (benzotriazol)-1-yloxytris(dimethylaminophosphonium hexafluorophosphate) or a reactive derivative of (II), such as acylchloride, acylimidazole, acylazide corresponding to acid (II) or an active ester, such as 2,4,5 trichlorophenoxyester or N-oxysuccinimidoester of acid (II) or

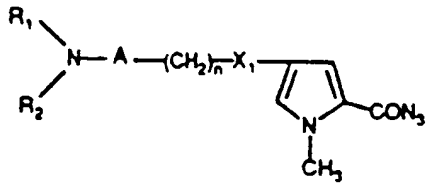
its anhydride.

The reaction of (II) with (III) is preferably carried out at molar ratios from 1:1 to 1:3 in an inert organic solvent, such as dimethylsulphoxide, hexamethylphosphorotriamide, dimethylacetamide or preferably dimethylformamide, in the presence of a condenser of the type mentioned above and of N-hydroxybenzotriazole or BOP and in the presence of an organic base, such as triethylamine, diisopropylethylamine and 1,8-bis-(dimethylamino)-naphthalene.

The reaction temperature may range from -10°C to 50°C and the reaction time from 2 to 48 hrs.

The reaction of compound as per formula (II) with compound as per formula (III) may also be conducted with a reactive derivative of compound as per formula (II) of the type mentioned above in a water-organic solvent biphasic system as for the amidation according to Schotten-Baumann, or in an organic solvent such as benzene, toluene, halogenated hydrocarbons, ethanol, methanol, tetrahydrofuran, dioxane, dimethylformamide, or in aqueous dioxane, ethanol, methanol. The reaction may be carried out also in the presence of an inorganic base, such as a hydroxide, a carbonate or a bicarbonate of an alkali metal, preferably sodium, potassium or barium or an organic base, such as triethylamine, diisopropylethylamine, pyridine or N,N-dimethylaminopyridine. The reaction is usually conducted at ambient temperature and the time required ranges from 2 to 24 hrs.

In process (b) a reactive precursor of compound as per formula (IV) may be e.g. compound having formula (VI)

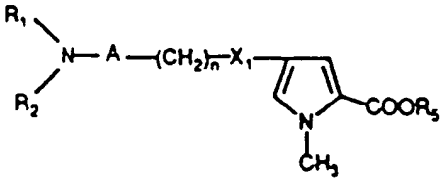


(VI)

The reaction of an isocyanate as per formula (IV) with an amidino acid as per formula (V) is preferably conducted with an acylazide as per formula (VI) as a reactive precursor of an isocyanate as per formula (IV). The reaction may be carried out in an aromatic hydrocarbon as solvent, such as for example benzene or toluene at 50°C-100°C for 5-20 hrs. A molar quantity of an organic base, e.g. triethylamine, pyridine, and the like, may be utilized in the reaction to salify an acid as per formula (V). The process of formation of an isocyanate from a reactive precursor, e.g. an acylazide, is well known in organic chemistry (cf. Curtius's reaction).

An azide as per formula (VI) may be prepared by causing to react compound as per formula (II) with diphenylphosphorazide or sodium azide (NaN_3).

In process (a) compound as per formula (II), where X_1, n, A, R_1 and R_2 are as defined above, may be prepared by hydrolysis of compound as per formula (VII)

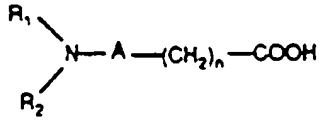


(VII)

where R_5 is a typical protective group of carboxylic acids, such as methyl, ethyl, t-butyl, benzyl, 2-trimethylxylylethyl, 2,2,2-trichloroethyl. The hydrolysis of compound as per formula (VII) may be performed according to the methods and procedures known in organic chemisty, as, for instance, referred to in T.W. Greene, Protective Groups in Organic Synthesis, J. Wiley and Sons, Interscience Publishers, 1981.

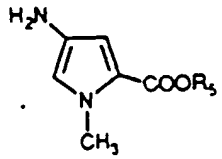
In particular, compound as per formula (II), where X_1, n and A are as defined above and R_1 and R_2 are equal and stand for a C_2–C_4 alkyl group substituted in position 2 by a halogen or an $-OSO_2R_4$ group, where R_4 is as defined above, may be prepared, if preferred so, by causing compound as per formula (II), where X_1, n and A are as defined above and R_1 and R_2 are equal and stand for a C_2-C_4 alkyl group substituted in position 2 by a hydroxy group, to react with a halogenating agent, e.g. $SOCl_2$ or $POCl_3$ or CH_3SO_2Cl/pyridine, to form compounds as per formula (II), where R_1 and R_2 are equal and stand for a C_2-C_4 alkyl group substituted in position 2 by a halogen, e.g. chlorine; or with a sulphonic acid reactive derivative as per formula R_4SO_3H, such as the corresponding chloride or anhydride, to form compounds as per formula (II), where R_1 and R_2 are equal and stand for a C_2-C_4 alkyl group substituted in position 2 by an $-OSO_2R_4$ group.

A compound as per formula (VII), where X_1 = -CONH-, R_1, R_2, R_5, n and A are as defined above (excepting when R_1 = H and R_2 = $-CO-(CH_2)_m-R_3$) may be prepared by causing compound as per formula (VIII)



(VIII)

where A, n, R_1 and R_2 are as defined above (excepting when R_1 = H and R_2 = $-CO-(CH_2)_m-R_3$) or a reactive derivative of same, to react with compound as per formula (IX)



(IX)

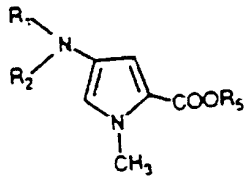
where R_5 is as defined above.

An acid reactive derivative as per formula (VIII) may be the same as that reported hereinabove for compound as per formula (II) and the reaction may be carried out under conditions analogous to those reported for the amidation of compound as per formula (II) with compound as per formula (III).

Compounds as per formula (VIII) are either known or prepared on the basis of classical procedures of organic chemistry starting from known compounds, as shown e.g. in J. Med. Chem., 32, 774 (1989) or J. Org. Chem., 26, 4996 (1961) or J. Med. Chem., 33, 1177 (1990).

Compounds as per formula (IX), where R_5 is as defined above are either known [cf. e.g. J. Org. Chem., 46, 3492 (1981)] or may be prepared on the basis of standard procedures starting from known compounds as shown e.g. in Tetr., 34, 2389 (1978).

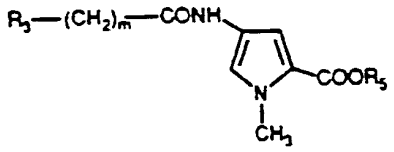
Compounds as per formula (VII), where R_1 and R_2 are as defined under i) and ii) and X_1 is a single chemical bond, A is a single chemical bond and n = 0, i.e. compounds as per formula (X)



(X)

where R_1, R_2 and R_5 are as defined above, are either known [cf. e.g. J. Med. Chem., 32, 774 (1989)] or prepared on the basis of standard procedures starting from known compounds.

Compounds as per formula (VII), where R_1 and R_2 are as defined under iii) and X_1 and A are both simple chemical bonds and n = 0, i.e. compounds as per formula (XI)

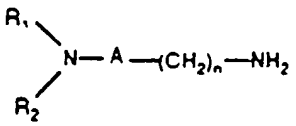


(XI)

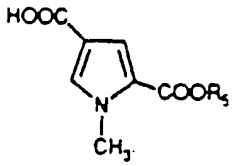
where m, R_3, and R_5 are as described above, may be prepared either on the basis of standard chemical procedures as e.g. described for the amidation reaction of compound as per formula (II) with compound as per formula (III) or as described in J. Med. Chem., 31, 341 (1988).

Compound as per formula (VII), where X_1 = -NHCO-, n, A, R_1 and R_2 are as defined above (excepting when R_1 = H and R_2 = $-CO-(CH_2)_m-R_3$) may be prepared by causing to react compound as per formula (XII)

with compound as per formula (XIII)



(XII)



(XIII)

where n, A, and R_5 are as defined above.

Amidation of compound (XII) with compound (XIII) may be performed under conditions analogous to those reported for the reaction between compound as per formula (II) with compound as per formula (III).

Compounds as per formula (XII) are either known or may be prepared on the basis of methods described e.g. in J. Med. Chem., 33, 112 (1990).

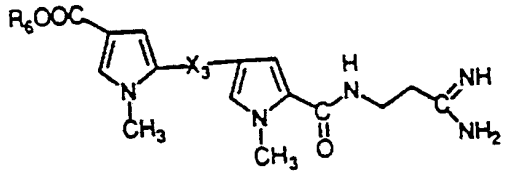
Compound as per formula (XIII), where R_5 is as defined above is either known or may be prepared on the basis of methods already known [(J. Org. Chem., 43, 4849 (1978); 51, 3125 (1986)].

Compound as per formula (III), where X_3 is -CONH-, is either known or may be prepared as described e.g. in J. Org. Chem., 50, 3774 (1985); compound as per formula (II), where H_3 is -NHCO- may be prepared as disclosed in the applicant's Italian Patent N. 22154 and referred to here for reference.

In process (ii), compound as per formula (IV) may be prepared from a corresponding reactive precursor as per formula (VI) on the basis of Curtius's reaction. An acylazide as per formula (VI) may be prepared from the corresponding acid as per formula (II) on the basis of the

methods described in Tetr., 30, 2151 (1974).

Compound as per formula (V) may be obtained by reductive lysis of the ester group of compound as per formula (XIV)

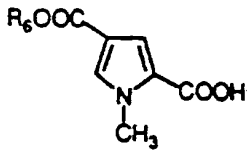


(XIV)

where R_6 is a protective group for a carboxylic acid, such as for example 2,2,2 trichloroethyl, benzyl, phenacyl, and the like, and X_3 is as already defined.

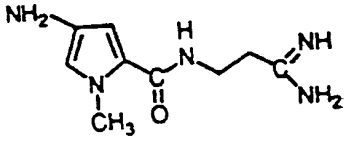
The R_6 group may be removed e.g. with Zn in acetic acid or by catalytic hydrogenation on Pd/C in H_2O, MeOH, EtOH, formic acid and their mixtures.

Compound as per formula (XIV), where X_3 = -CONH-, may be prepared by causing to react compound as per formula (XV)



(XV)

where R_6 is as defined above, or a reactive derivative of same, with compound as per formula (XVI)

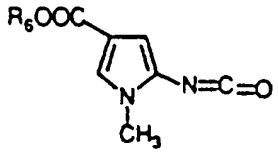


(XVI)

A reactive derivative of compound (XV) may be of the same type as those reported for compounds as per formula (II) and the amidation reaction between (XV) and (XVI) may be carried out as reported above for the reaction between compounds as per formulas (II) and (III).

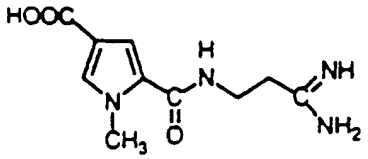
Compounds as per formulas (XV) and (XVI) may be prepared as disclosed in the applicant's Italian Patent N. 22154 dated 22nd Nov. 1990 and referred to here for reference.

Compounds as per formula (XIV), where X_3 = -NHCO- may be prepared by causing to react compound as per formula (XVII)



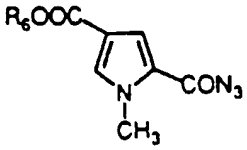
(XVII)

where R_6 as defined above, or an active precursor of same, with compound as per formula (XVIII)



(XVIII)

A reactive precursor of compound (XVII) may be a compound as per formula (XIX)



(XIX)

where R_6 is as defined above.

The reaction of an isocyanate as per formula (XVII) with an acid as per formula (XVIII) may preferably be conducted using an azide as per formula (XIX) as reactive precursor of (XVII) under conditions analogous to those reported above for the reaction of compound as per formula (VI) with compound as per formula (V).

Compounds as per formulas (XVIII) and (XIX) may be prepared as disclosed in the applicant's Italian Patent N. 22154 dated 22nd Nov. 1990 and referred to here for reference.

The present invention further refers to pharmaceutical compositions containing as active ingredient a compound as per formula (I) or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable vector or diluent.

A therapeutically effective amount of compound as per formula (I) according to the invention is combined with an inert and pharmaceutically acceptable vector. The vectors used may be the traditional ones and the compositions may be formulated according to the usual methods. The compounds as per the present invention are useful for the therapeutic treatment of humans and animals. In particular, the compounds as per the invention are useful as antitumoural and/or antiviral agents when administered in therapeutically effective amounts, e.g. an adequate dosage for adult administration may range from 0.1 to 100 mg approx. pro dose from 1 to 4 times/day.

The following examples further illustrate the claimed invention.

These examples are illustrative only; in no event are they to be regarded as limiting the scope of the invention.

EXAMPLE 1

1-Methyl-4-[4-[N,N bis(2-hydroxyethyl)-amino]benzeneaminocarbonyl]pyrrole-2-carboxylic acid methyl ester (VII, X_1 = -NHCO-, A = p-phenylene, n = 0, R_1 = R_2 = 2-hydroxyethyl, R_5 = CH_3)

A solution of N,N bis(2-hydroxyethyl)1,4-phenylendiamine (XII, A = p-phenylene, n = 0, R_1 = R_2 = 2-hydroxyethyl) (0.87 g; 4.42 mM), prepared as described in J. Med. Chem., 33, 112 (1990) in MeOH (40 ml) was added with a benzene solution (30 ml) of 1-methyl-2-carbomethoxy-4-pyrrolecarboxylic acid (XIII, R_5 = methyl) (1.8 g; 8.85 mM) obtained from (XIII) (1.6 g; 8.85 mM) by reflux with $SOCl_2$ (4.5 ml; 62 mM) in benzene (120 ml).

After a 1-hr stirring at ambient temperature, the reaction mixture was evaporated to dryness and the residue was separated by chromatography on silica gel (eluent CH_2Cl_2/MeOH 9/1) to form 1.35 g of product (VII, X_1 = -NHCO-, A = phenylene, n = 0, R_1 = R_2 = 2-hydroxyethyl, R_5 = methyl) (yield 84%).

^{1}H-NMR MeOH-d_4 δ: 3.70 (t, 4H); 3.87 (t, 4H); 3.99 (s, 3H); 4.13 (s, 3H); 6.90 (d, 2H); 7.56 (d, 2H); 7.61 (d, 1H); 7.73 (d, 1H).

EXAMPLE 2

1-Methyl-4-[4-[N,N-bis(2-hydroxyethyl)-amino]benzeneaminocarbonyl]pyrrole-2-carboxylic acid (II, X_1 = -NHCO-, A = p-phenylene, n = 0, R_1 = R_2 = 2-hydroxyethyl)

A solution of VII (X_1 = -NHCO-, A = p-phenylene, n = 0, R_1 = R_2 =

2-hydroxyethyl, R_5 = methyl) 0.53 g; 1.46 mM) in MeOH (3 ml) and 10% NaOH aqueous solution (2.5 ml) was refluxed for 3 hrs, concentrated to small volume, acidified with HCl 1 N to a pH equal to 6, and evaporated to dryness. The residue was taken up with cold MeOH, centrifuged, and evaporated to dryness to form 460 mg of II (X_1 = -NHCO-, A = p-phenylene, n = 0, R_1 = R_2 = 2-hydroxyethyl) (yield 91%).

^{1}H-NMR DMSO-d_6 δ: 3.36 (t, 4H); 3.52 (t, 4H); 3.89 (s, 3H); 6.61 (d, 2H); 7.12 (d, 1H); 7.37 (d, 1H); 7.49 (d, 2H); 9.27 (s, 1H).

EXAMPLE 3

1-Methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]benzeneamino-carbonyl]pyrrole-2-carboxylic acid (II, X_1 = -NHCO-, A = p-phenylene, n = 0, R_1 = R_2 = 2-chloroethyl)

A solution of II (X_1 = -NHCO-, A = p-phenylene, n = 0, R_1 = R_2 = 2-hydroxyethyl) (0.38 g; 1.09 mM) in anhydrous pyridine (15 ml) cooled to 0°C-5°C was added with methanesulphonyl chloride (0.5 ml; 6.46 mM).

After a 1-hr stirring at ambient temperature and 1½ hr at 75°C, the reaction mixture was evaporated to dryness and the residue was chromatographed on silica gel (eluent $CHCl_3$ 85/MeOH 15) to form 167 mg of II (X_1 = -NHCO-, A = p-phenylene, n = 0, R_1 = R_2 = 2-chloroethyl) (yield 40%).

^{1}H-NMR DMSO-d_6 δ: 3.6-3.75 (m, 8H); 3.85 (s, 3H); 6.69 (d, 2H); 7.34 (d, 1H); 7.53 (d, 2H); 7.56 (d, 1H).

EXAMPLE 4

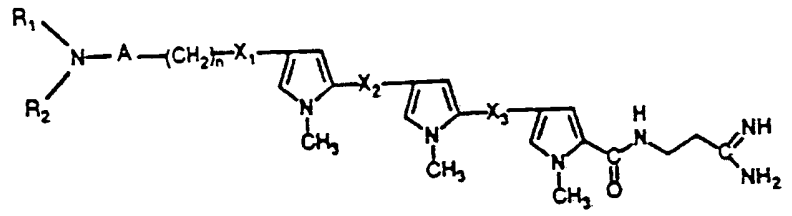
3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]benzeneaminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride (I, X_1 = -NHCO-, X_2 = X_3 = -CONH-, n = 0, A = p-phenylene, R_1 = R_2 = 2-chloroethyl)

A solution of II (X_1 = -NHCO-, A = p-phenylene, n = 0, R_1 = R_2 = 2-chloroethyl) (0.172 g; 0.447 mM) in anhydrous dimethylformamide (10 ml) was added in the order with 190 mg of 1-methyl-4-(1-methyl-4-aminopyrrole-2-carboxyamido)-pyrrole-2-carboxyamidoproprionamidino hydrochloride (III, X_3 = -CONH-) (190 mg; 0.469 mM), 63 mg of N-hydroxybenzotriazole (HOBT) (0.469 mM), 103 mg of 1,8-bis-(dimethylamino)-naphthalene (0.480 mM) and by subsequent additions [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (162 mg; 0.848 mM). After a 1-hr stirring at ambient temperature the reaction mixture was evaporated to dryness and the residue was chromatographed on silica gel (eluent $CHCl_3$/EtOH 98% 6/4) to form 139 mg of I (X_1 = -NHCO-, X_2 = X_3 = -CONH-, n = 0, A = p-phenylene, R_1 = R_2 = 2-chloroethyl) (yield 42%).

^{1}H-NMR DMSO-d_6 δ: 2.63 (t, 2H); 3.50 (q, 2H); 3.81 (s, 3H); 3.86 (s, 3H); 3.92 (s, 3H); 6.23 (d, 2H); 6.95 (d, 1H); 7.05 (d, 1H); 7.18 (d, 1H); 7.24 (d, 1H); 7.41 (d, 1H); 7.53 (d, 2H); 7.69 (d, 1H); 8.19 (t, 1H); 9.50 (s, 1H); 9.53 (bs, 2H); 9.90 (s, 1H); 9.92 (bs, 2H); 10.09 (s, 1H).

CLAIMS

1 1. Compounds as per general formula (I)



2 where:

3 n = 0 or a whole number from 1 to 6

4 A = a single chemical bond or an alicyclic or aromatic or

5 heterocyclic residue,

6 X_1 = a chemical bond, the -NHCO- group or the -CONH- group

7 X_2, X_3 (either equal or different) = the -CONH- or -NHCO- group

8 and where:

9 i) R_1 and R_2 (equal) = an oxiranomethyl or 1-aziridinomethyl or C_2-

10 C_4 alkyl group, substituted in position 2, if required, by a hydroxy

11 or C_2-C_4 alcoxy halogen or $-OSO_2R_4$ group, where:

12 R_4 is C_1-C_4 alkyl or phenyl

13 or

14 ii) R_1 = H, R_2 as defined above

15 or

16 iii) R_1 = H, R_2 = $-CO-(CH_2)_m-R_3$, where m is 0 or a whole number from

17 1 to 4 and R_3 = halogen, oxiranyl or methyloxiranyl or azirinidyl,

18 cyclopropyl or a C_2-C_6 alkenyl group substituted, if required, by

19 halogens or a ketone or an α,β unsaturated alicylic lactone.

20 Considering that:

if R_1 and R_2 are as defined under i) and ii) and X_1 is a single chemical bond, A is a single chemical bond and n = 0;

if R_1 and R_2 are as defined under iii), X_1 and A are single chemical bonds and n = 0;

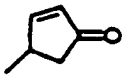
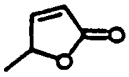
if X_1 is a single chemical bond or the -CONH- group and n = 0, X_2 = X_3 = -CONH- is impossible.

2. Compounds according to claim 1 wherein:

n is as defined above

A is a single cyclohexyl or p-phenylene or 1-methylpyrrole or thiophene or thiazole or imidazole or furan or isoxazole or oxazole or triazole or pyridine or pyrrole chemical bond

R_1 and R_2 (when R_2 is not $-CO-(CH_2)_m-R_3$) preferably stand for an ethyl or 2-chloroethyl or methanesulfonylethyl and when R_2 = $-CO-(CH_2)_m-R_3$, R_3preferably stands for chlorine or bromine, or a 3-methyloxyranyl or ethenyl or 1-chloroethenyl or 1-bromoethenyl group

 ,  .

where:

m = 0, 1, 2,

X_1, X_2, X_3 are as defined above.

3. Compounds as per formula (I) according to claims 1 and 2 within the group:

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]benzenecarboxyamido]pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]benzeneaminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]benzeneaminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]benzenecarboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]thiophene-2-carboxyamido]pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-methyl-4-[N,N-bis(2-chloroethyl)-amino]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[N,N-bis(2-chloroethyl)-amino]pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[N,N-bis(2-chloroethyl)-amino]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[N,N-bis(2-chloroethyl)-amino]pyrrole-2-aminocarbonyl]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[6-[4-[N,N-bis(2-chloroethyl)-amino]phenyl]hexaneaminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-(3-methyloxirano-carbonylamino)pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-(cyclopropylcarbonylamino)pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[1-aziridino) carbonylamino]pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-(α-chloroacrylamido)pyrrole-2-carboxyamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[2[4-[N,N-bis(2-chloroethyl)-amino]phenyl]ethanaminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido] propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[N,N-bis(2-chloroethyl)-amino]benzylaminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

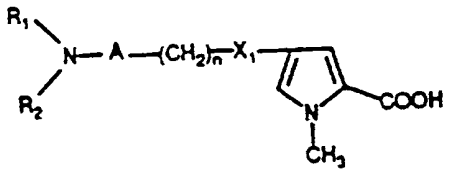
3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[3-[4-[N,N-bis(2-chloroethyl)-amino]-phenyl]propanamino-carbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

3-[1-Methyl-4-[1-methyl-4-[1-methyl-4-[4-[4-[N,N-bis(2-chloroethyl)-

amino]-phenyl]butanamido]pyrrole-2-aminocarbonyl]pyrrole-2-carboxyamido]pyrrole-2-carboxyamido]propionamidino hydrochloride;

N-deformyl-N-[4-[4-[N,N-bis(2-chloroethyl)amino]phenyl] butanoyl]dystamicin hydrochloride.

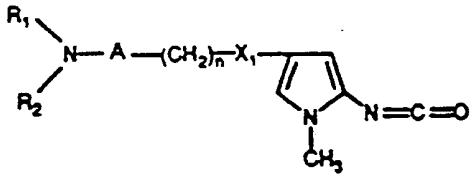
4. Compounds as per general formula (II)



(II)

where X_1, n, A, R_1 and R_2 are as defined in claims 1 and 2.

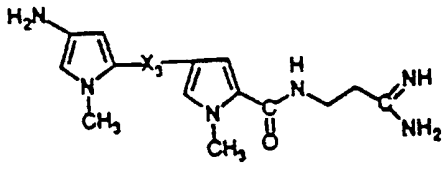
5. Compound as per formula (IV)



(IV)

where X_1, n, A, R_1 and R_2 are as defined in claims 1 and 2.

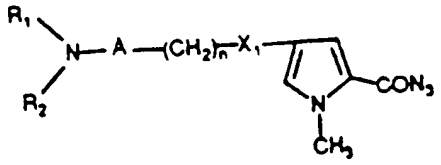
6. Compound as per formula (V)



(V)

where X_3 is -CONH- or -NHCO-.

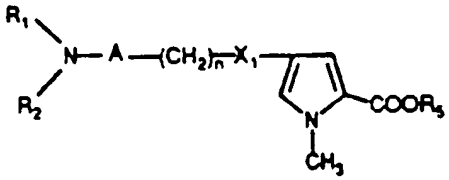
7. Compound as per formula (VI)



(VI)

where X_1, n, A, R_1 and R_2 are as defined in claims 1 and 2.

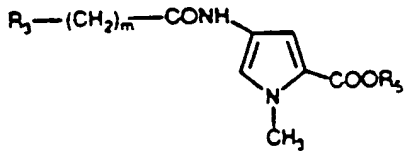
8. Compound as per formula (VII)



(VII)

where n and A are as defined above, X_1 stands for -CONH- or -NHCO-, R_1 and R_2 are as defined under i) and ii) of claim 1, and R_5 is a protective group of a carboxylic acid.

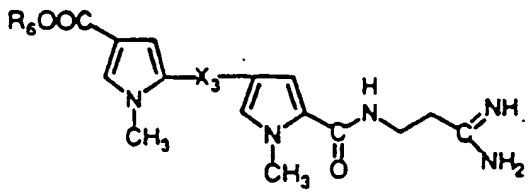
9. Compound as per formula (XI)



(XI)

where m and R_3 are as defined in claims 1 and 2 and R_5 is a protective group of a carboxylic acid.

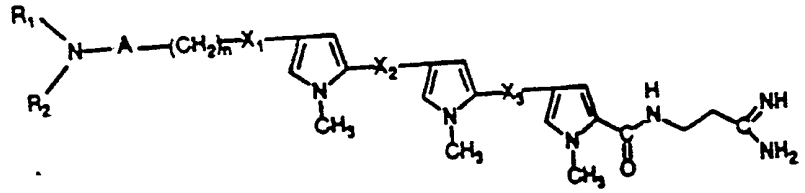
10. Compound as per formula (XIV)



(XIV)

where X_3 is -CONH- or -NHCO- and R_6 is a protective group of a carboxylic acid.

11. Process for the preparation of compounds as per formula (I)



(I)

where

n = 0 or a whole number from 1 to 6

A = a single chemical bond or an alicyclic or aromatic or heterocyclic residue,

X_1 = a chemical bond, the -NHCO- group or the -CONH- group

X_2 = the -CONH- group and X_3 = the -CONH- or -NHCO- group

and where:

i) R_1 and R_2 (equal) = an oxiranomethyl or 1-aziridinomethyl or C_2-C_4 alkyl group, substituted in position 2, if required, by a hydroxy or C_2-C_4 alcoxy halogen or an $-OSO_2R_4$ group, where:

R_4 is C_1-C_4 alkyl or phenyl

or

ii) R_1 = H, R_2 as defined above

or

iii) R_1 = H, R_2 = $-CO-(CH_2)_m-R_3$, where m is 0 or a whole number from 1 to 4 and R_3 = halogen, oxiranyl or methyloxiranyl or azirinidyl, cyclopropyl or a C_2-C_6 alkenyl group substituted, if required, by

halogens or a ketone or an α,β unsaturated alicylic lactone.

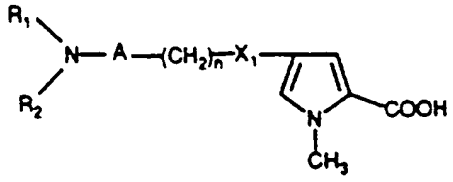
Considering that:

if R_1 and R_2 are as defined under i) and ii) and X_1 is a single chemical bond, A is a single chemical bond and n = 0;

if R_1 and R_2 are as defined under iii), X_1 and A are single chemical bonds and n = 0;

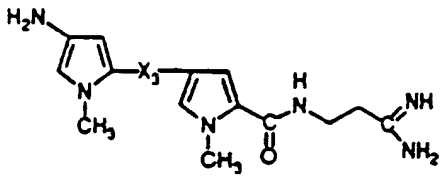
if X_1 is a single chemical bond or the -CONH- group and n = 0, X_2 = X_3 = -CONH- is impossible,

based on the reaction of compound as per formula (II)



(II)

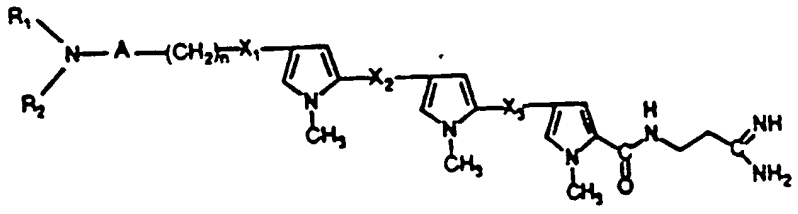
where n, A, R_1, R_2 and X_1 are as defined above, or a reactive derivative thereof, with compound as per formula (III)



(III)

where X_3 is as defined above.

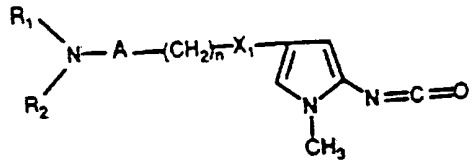
12. Process for the preparation of compounds as per formula (I)



(I)

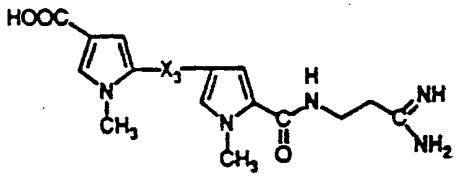
where n, A, X_1, X_3, R_1 and R_2 are as defined in claim 11 and X_2 is the -NHCO-

based on the reaction of compound as per formula (IV)



(IV)

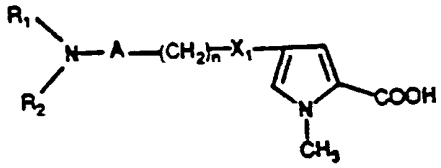
where n, A, X_1, R_1 and R_2 are as defined above, or a reactive precursor thereof, with compound as per formula (V)



(V)

where X_3 is as defined in claim 11.

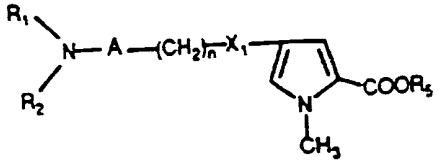
13. Process for the preparation of compound as per formula (II)



(II)

where n, A, R_1 and R_2 are as defined in claim 11 and X_1 is a chemical bond, the -NHCO- group or the -CONH- group

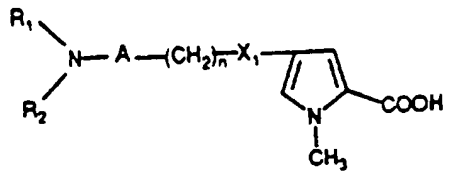
based on the hydrolysis of compound as per formula (VII)



(VII)

where n, A, X_1, R_1 and R_2 are as defined above and R_5 is a protective group of carboxylic acids.

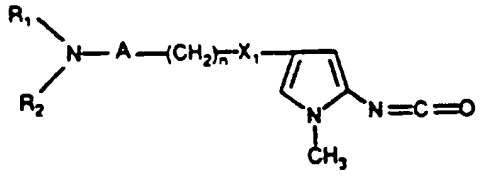
14. Process for the preparation of compound as per formula (II)



(II)

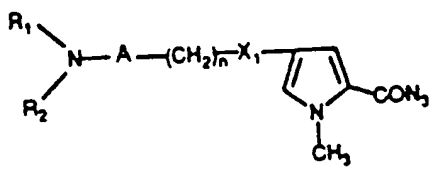
where n, A, X_1 are as defined in claim 11 and R_1 and R_2 are equal and stand for a C_2-C_4 alkyl group substituted in position 2 by a halogen or a $-OSO_2R_4$ group, where R_4 = C_1-C_4 alkyl or phenyl, based on the reaction of compound as per formula (II), where n, A, and X_1 are as defined above and R_1 and R_2 are equal and stand for a C_2-C_4 alkyl group substituted in position 2 by a hydroxy group, with a halogenating agent or a reactive derivative of an acid as per formula R_4SO_3H.

15. Process for the preparation of compound as per formula (IV)



(IV)

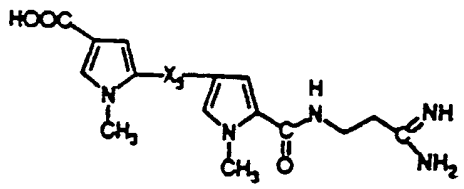
where n, A, X_1, R_1 and R_2 are as defined in claim 11, based on the rearrangement of azides as per formula (VI)



(VI)

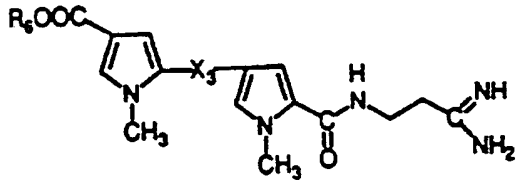
where n, A, X_1, R_1 and R_2 are as defined above, at 50°C-100°C in the presence of an organic base.

16. Process for the preparation of compound as per formula (V)



(V)

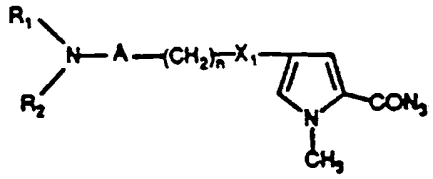
where X_3 = -NHCO- or -CONH- by reductive lysis of compound as per formula (XIV)



(XIV)

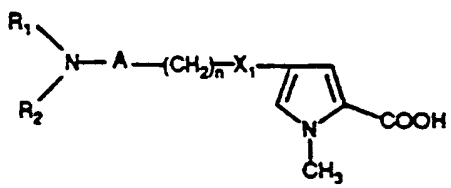
where X_3 is as defined above and R_6 is a protective group of carboxylic acids.

17. Process for the preparation of compound as per formula (VI)



(VI)

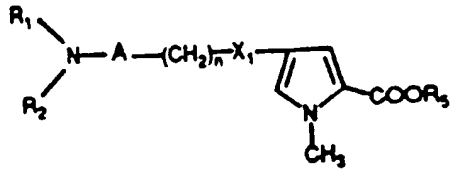
where n, A, X_1, R_1 and R_2 are as defined in claim 11 by causing compounds as per formula (II)



(II)

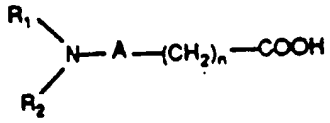
where n, A, X_1, R_1 and R_2 are as defined above, to react with diphenylphosphorazide or sodium azide (NaN_3).

18. Process for the preparation of compound as per formula (VII)



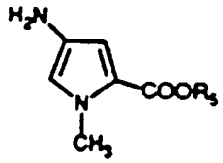
(VII)

where n, A, R_1 and R_2 are as defined in claim 11 and X_1 is the -CONH- group, based on the reaction of compound as per formula (VIII)



(VIII)

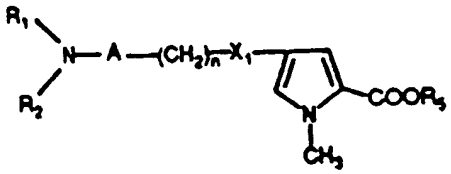
where n, A, R_1 and R_2 are as defined above, or a reactive derivative thereof, with compound as per formula (IX)



(IX)

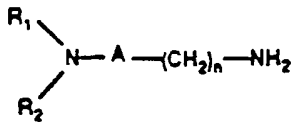
where R_5 is a protective group of a carboxylic acid.

19. Process for the preparation of compound as per formula (VII)



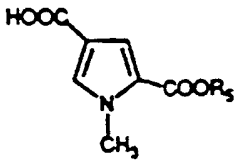
(VII)

where n, A, R_1 and R_2 are as defined in claim 11 and X_1 is the –NHCO– group, by causing compound as per formula (XII)



(XII)

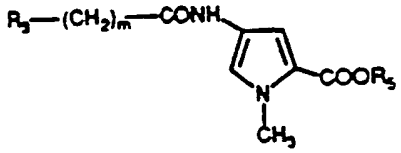
where n, A, R_1 and R_2 are as defined above, to react with compound as per formula (XIII)



(XIII)

where R_5 is a protective group of a carboxylic acid, or with a reactive derivative thereof.

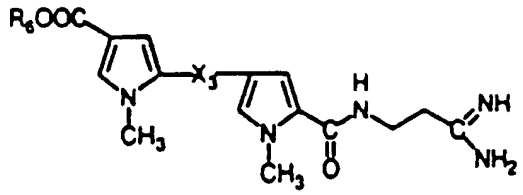
20. Process for the preparation of compound as per formula (XI)



(XI)

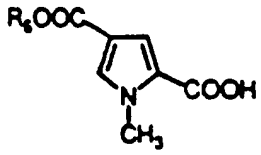
where R_3 = halogen, oxiranyl or methyloxiranyl or azirinidyl, cyclopropyl or a C_2-C_6 alkenyl group substituted, if required, by halogens or a ketone or an α,β unsaturated alicylic lactone, m = 0 or a whole number between 1 and 4, and R_5 is a protective group of a carboxylic acid, by causing the corresponding acid and amine precursors to react under the traditional amidation conditions.

21. Process for the preparation of compound as per formula (XIV)



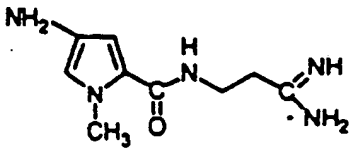
(XIV)

where X_6 = -CONH- and R_6 is a protective group of a carboxylic acid, based on the reaction of compound as per formula (XV)



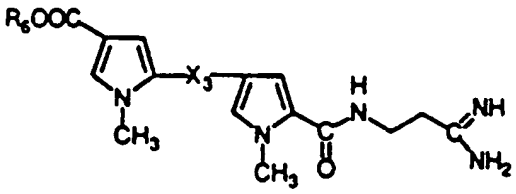
(XV)

where R_6 is as defined above, or a reactive derivative thereof, with compound as per formula (XVI)



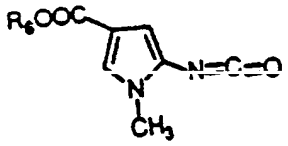
(XVI)

22. Process for the preparation of compound as per formula (XIV)



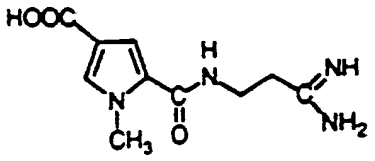
(XIV)

where X_3 = -NHCO- and R_6 is a protective group of a carboxylic acid, based on the reaction of compound as per formula (XVII)



(XVII)

where R_6 is as defined above, or a reactive derivative thereof, with compound as per formula (XVIII).



(XVIII)

23. Use of compounds according to claims 1 to 3 for the preparation of pharmaceutical compositions.

24. Pharmaceutical compositions whose active ingredient is a compound according to claims 1 to 3 and a pharmaceutically acceptable vector or diluent.

25. Pharmaceutical compositions according to claim 24 as anticancer agents.

26. Pharmaceutical compositions according to claim 24 as antiviral agents.

27. Method for the treatment of tumoural diseases, envisaging the administration of pharmaceutical compositions whose active principle is a compound according to claims 1 to 3 in amounts ranging from 0.1 to 100 mg pro dose from 1 to 4 times/day and a pharmaceutically acceptable vector or diluent.

28. Method for the treatment of viral diseases, envisaging the administration of pharmaceutical compositions whose active principle

is a compound according to claims 1 to 3 in amounts ranging from 0.1 to 100 mg pro dose from 1 to 4 times/day and a pharmaceutically acceptable vector or diluent.